Gottesman, Michael M. 2016 B

Dr. Michael M. Gottesman Oral History 2016 B

Download the PDF: Gottesman_Michael_Oral_History_2016_B (PDF 90 kB)

Part 2 of 2:

Well, my hope was to go back to the laboratory [laughs]. At that point I was chief of the laboratory of sub-biology at NCI. We spoke about that a little bit. And I thought it would be nice to go back full time but that didn't last very long. So, you may recall that Bernadine Healy was director for not much more than a year or less than a year I think. And immediately after the new administration came in -- the Clinton administration -- they were interested in naming a new director and very quickly Harold Varmus' name came to the floor. And it became pretty clear that he would probably be approved by the Senate as a new director of NIH. And he began -- because he was limited in what he could do at the NIH -- he began to do some due diligence and he approached me and we talked a little bit about the future of the intramural program. He had known about my role in genome and he knew my science as well. I mean, we had over the years interacted on many occasions. In fact, Harold and Mike Bishop had written an editorial piece for the New York Times about multi-drug resistance and about how this was a great example of how basic science could contribute to the possible cure of cancer. It was overly optimistic but it was a nice, positive response to our work. So, during the interim period when there was no director at NIH Ruth Kirschstein was the acting director and Congress had in the meantime announced that they wanted a review of what they call the role and the size and the cost of the intramural program. This was actually the last Congressional demand for that kind of review and it was taken quite seriously at NIH and committees were set up to first of all, outside committee to do the review and an internal committee to feed information and data. And I, together with Jay Moskowitz -- now Jay you may recall was the principal deputy for a while and then was also the deputy for I think what was called Science Policy and Technology Transfer. And so he was an actual extramural. And extramural and not that involved with the intramural program. So, I quickly sort of became the titular chairman of that committee and began a series of meetings with the scientific directors to be able to respond to what was called the Marks-Cassell Committee after Gail Cassel and Paul Marks who were chairs of that committee. It was a really outstanding group of people some of whom had had experience with NIH before and some of whom were just senior faculty who were coming in to review the role, size, the cost of the intramural program. It was an opportunity for me to learn a lot about the intramural program at large. I mean, I knew some of the details. I knew about genome. At that point I had been Acting Scientific Director of genome and I had been an NCI Lab Chief. So, we got together with the committee. We met on at least half a dozen occasions. Committee came out and we provide3d the data that they needed to make recommendations. They made some very far- reaching recommendations that have actually been sort of the blue print for all the changes that were made at that point in the intramural program. I would say -- I was trying to think back as to why Congress was interested then in the intramural program -- I think there was a sense that the initial transcendency of the intramural program was starting to fade, that the extramural program was beginning to become more important. And I think Congress rightfully wanted to know whether this was an investment worthy of making. So we had discussions both about the clinical program, about the laboratory science. And when Harold became director, which was probably around October -- I don't know precisely -- of '93 he asked me to become Deputy Director for Intramural Research and to help him put together the implementation of the advice that we had gotten from the Marks-Cassell committee. Which I did with great enthusiasm because I had been sort of involved in the discussions with them about directions we wanted to go. So we pretty dramatically revised the process for tenure at the NIH. It had been a process that was managed by the scientific directors and there was a sense that the scientific directors would never say no to a candidate that came from another scientific director so we wanted a central committee that was a peer-based committee that would assure very high quality. And very quickly we began to realize that not every candidate put forward was of the quality that you'd want to have in the intramural program. We also had developed over time a set of investigators that I think could best be called collaborative investigators. And this had actually been noticed by Dinah Singer who had been asked previously -- and I was involved in this committee, which Rick Klausner was involved in as well -- to sort of evaluate what was going on intramurally.

And the sense was that we had probably a small majority of true independent senior investigators and a lot of people who had been chosen by the senior investigators to be tenured scientists who were not really, in fact, as independent and as outstanding as the ones who had made the NIH intramural program as great as it really was. So, we had to deal with the fact that we had a lot of people who were not exactly senior investigators in the real sense. And many of them there were individual analyses. Some of them turned out to be high quality were grandfathered into the tenure process. And others became a position that we had created called staff scientist. And that was the origin of the staff scientist position, which has become really quite successful. NIH has about 1300 staff scientists, which is more than the number of PIs that we have. They support the core facilities at NIH and support many of the larger laboratories at the NIH. And it's a program that recently there was a review of the demographics of the NIH workforce and one of the recommendations was that we develop the staff scientist position as a position not just at the NIH but that there find -- that we find means of support going outside into extramural communities.

And in fact NCI is now piloting a program, which they're putting together to provide support -- relatively long term support -- for people to be staff scientists within an academic context as well. Part of this is in response to the fact that we are producing far more outstanding scientists than we have independent physicians for. And so finding appropriate places for people to work, to enjoy the science, and to support existing programs made a lot of sense and that was begun way back in the early 1990s in the intramural program. There were changes in the way we review our science. Absolute requirement that all of the independent scientists -- science at NIH be reviewed by an outside board of scientific counselors and a very sort of rigorous oversight process which was led by my office to assure that people follow the rules and that scientists who weren't doing well would have resources adjusted or eliminated. And actually, the turnover of intramural scientists is much greater than most people appreciate. Every ten years about 500 scientists stop being senior investigators. The resources turn over and new investigators are required. So, with a -- with a population of about 1,000 PIs that's pretty impressive turnover.

We needed to develop mechanisms to hire people that -- within the government system gave us flexibility and this is about title 42, an important recruitment mechanism. And we developed the tenure track. That was -- really didn't exist before people kind of fell into positions. I have to say my own position at NIH was kind of -- I was put up for tenure by NCI and immediately became a tenured scientist, as did my wife. Nowadays that doesn't happen so simply. There's a long, pretty rigorous process of evaluation before people are tenured at the NIH.

So, he's amazingly smart person. He always -- it always astonished me that he could sit through most complicated seminars and no matter what the subject was have a really intelligent question. He -- and probing question. You know, that got really to the heart of the issue. So, his intellect was -- I think at the NIH even, which had a lot of really smart people -- was unchallenged. And it was by virtue of that that I think he was great leader because he was respected by everyone.

And respected by the Congress partly because of his intellectual contributions and obviously having a Nobel Prize was not a minor thing. To have an NIH director with that kind of credential was really a positive thing. He was -- I would say very clearly did not suffer fools gladly. So I remember lots of meetings in which he, you know, if he felt the discussion was not at a level that satisfied him he would just get up and kind of walk away. We used to have staff meetings, which we knew were over when he would get up from the table and start to do his email. That was kind of interesting [laughs]. He had a, I think, a great sense of talent. He appreciated people who were really talented and people who were not. He wasn't particularly interested in administrative matters and either depended on other people to do them or tried as best he could to cut through bureaucratic detail. And some people will claim that some of the problems that NIH has now with the bureaucracy date from his decision not to pursue certain kinds of bureaucratic details [laughs]. And on the other hand, it was a way of getting a lot done in a sort of creative kind of way and science is I think a very delicate ecostructure. It needs to be led by people who are sensitive to scientific needs and who are willing sometimes to take some shortcuts to make sure people get the resources they need to do outstanding science. He was great to work for. I always knew -- he always made it clear what his goals were and I had no problem at least trying to interpret those as best I could in the intramural program.

So initially there was a principal deputy and then there was an extramural deputy and an intramural deputy and there was a deputy -- for a while there's been a deputy director for management. So those are the three -- other than the principal deputy those are the three that there is. Currently we have additional deputies. We have a deputy director for outreach and science policy -- science and science policy. That's Kathy Hudson currently.

So I meet weekly. We have executive committee meetings and then as needs arise I will meet with him and whoever of the -- of his immediate staff needs to be involved in decision making. I don't meet with him that much one on one. I used to meet with Harold one on one all the time because at the end of every day he would come into my office looking for chocolate and he would sit down and we would have a little bit of a chat about what was going on and so on and so forth. Francis is much more disciplined.

Well, the other thing is my office has moved. I mean, it used to be -- at the very first it was actually adjacent to the director's office. It was in the office currently housed by the deputy and then it moved around the corner to what is now a conference room. And then it moved a little bit down the hall. And then it moved to the wing which housed the deputy director for extramural. And that distance I think makes a difference in terms of the random likelihood that the director will walk in to have a conversation. So I actually miss the proximity to the director. It was quite nice [laughs].

So there are whole -- in terms -- in terms of what we call the front office the immediate office of the director. So it's not Dr. Collins, Dr. Kaback, Dr. Hudson. There are certain policy level decisions that are made at that level that affect both the extramural program and the intramural program. How those are interpreted extramurally and intramurally can be somewhat different. So, for example, I mean we recently had been discussing this issue of making sure that sex is considered as a biological variable in animal studies. So, the extramural program is pretty straightforward because people write grants and the grants can include information about that and that can be your requirement in order to get a grant that you need to specify. Intramurally because review is retrospective it's much more complicated in order to make sure that policy is being followed. And we tend to be -- we try to be flexible. As I mentioned before it's important for creative scientists to have some ability to make decisions on their own. But on the other hand, policy is policy and we need to be sure that people follow the rules. So there's usually an educational process. A rational case is made for why this is important for their science. We usually will pilot some efforts to try and figure out how best to get buy in. And then we develop a process which involves -- we have -- we do -- we have this oversight which involves risk management surveys so the scientific directors are ultimately responsible for the behavior of their scientists within their programs. And we make sure that the scientific directors have a checklist of things that they need to do to make sure people are behaving. For almost all policies that are not rigorous legal requirements I would say compliance in the intramural program is not 100 percent because there's variability in the extent to which the scientific directors exercise their authority. But, most things are pretty -- done pretty well. And my job is to oversee the overall compliance structure and make sure people are -- know what the expectations are, know what the consequences are, and follow the rules as best they can. When there are legal requirements or requirements that are regulatory our oversight is much tighter.

Right. So, this issue comes up all the time when we come up with a new policy and there's push back about that policy because it's a new bureaucratic requirement or because the rationale for it is not clear to the scientists. And by the way, the nature of scientists is they constantly question authority and the best scientists question it more than any others. So, Elias Zerhouni used to refer to this as herding squirrels. You know, you have to get them kind of heading in the same direction. And by the way, the solution to herding squirrels is to open the refrigerator. So that's -- gets them going in the right direction. And it works for all scientists actually [laughs]. And I don't mean food per say but funding for their research. It helps a lot to get things done. I would say that almost all the time when something comes up people will say to me, "Is this a legal requirement? A regulatory requirement? A departmental requirement? Or something at NIH that's policy that we can fight over, argue about?" And we try to, you know, be able to answer as clearly as possible and although policies, you know, have the force of authority behind them at the NIH the likelihood of 100 percent compliance becomes less as the statutory requirement dwindles. But, the whole business of taking 1,000 people who are creative scientists and getting them all moving in the same direction following the same set of rules is not a trivial job. It's probably the hardest part of my job.

Right. So, there are general principles that cover the conduct of research so within the laboratory setting there are absolute requirements that data that produced be rigorously produced, that it be reproducible, that the record keeping be absolutely top notch. So all of these are in the domain of research integrity. And that principle applies to everything that we do. Even history I would say, right, in terms of record keeping and reporting as accurately as you can what you find. In the clinical domain that's a whole other area that in addition to the basic principles of research integrity there are a whole variety of issues associated with clinical research and protection of human subjects that are really important. And at the NIH the provision of clinical care because we're taking care of sometimes very sick patients. So in addition to being research subjects they're also patients. And actually this issue is not a trivial one for research investigators because under a research protocol their primary responsibility is to follow that protocol. As clinicians their primary responsibility is to make sure that nobody is hurt in the conduct of the research. And occasionally those two are -- appear to be at least on the surface at odds with each other. You have a patient that's deathly ill and you want to enroll them in a protocol but they don't satisfy their requirements for that protocol and so you can't -- unless you have a specific exemption you can't just put a patient on a protocol. And occasionally we'll have an investigator who just said, "Well, I mean, I had this child and they would clearly benefit -- we think they would benefit from this new drug that we're testing. We'd love to put them on the protocol but we can't because they're not -- they're not the right age. The presentation of the disease is wrong. Something is different about the disease. So, the clinical part of what we do can be at odds with the absolute rigorous requirement that the research be done under controlled conditions that allow you to come up with real conclusions about whether the study design gives you the data that you want. And I think sometimes when we run into problems with behavior of our clinical investigators it has to do with that conflict of commitment and it's a -- it is another important part of my job to be able to reconcile those two things. That you can do top quality research in an environment that provides really outstanding clinical care as well.

Right. So there are compassion exemptions but a real case has to be made. I don't get involved that much in the -- so a lot of the decisions, particularly decisions that are FDA related are between the FDA and the IND holder. This is an area in flux. One of the questions that you kind of asked me was how things have changed in terms of clinical research. So, when I became deputy director for intramural research all the FDA compliance issues -- making sure the INDs were being properly recorded and data was being saved and information was being provided to the FDA was in the hands of either individual investigators or the institutes that were overseeing those investigators. And more and more it's become obvious that more oversight is needed at the central level, that we need to assure that everybody who holds an IND is properly managing it, reporting back, and making sure that everything is running smoothly. And I think one of the directions that we're going in is a little more central oversight of the interactions with he FDA. So, we're hoping that that will be a positive change and will assure even more rigorously that research done here is done at the highest standards and meet all the requirements of the FDA as well as our NIH requirements.

Right. You know, so the -- I think in general the FDA has become much more sensitive to the individual research requirements and we generally have a good -- really good relationship. The FDA is a sister agency. The NIH is sort of the flagship for clinical research in the country. We have many instances, for example, in which we learn together with the FDA how to regulate things. For example -- gene therapy, stem cell based therapies, and the FDA is learning itself what should be the requirements for growing cells for introducing them into patients, for studying the outcome of that. And we are more than eager to sort of work with them to figure out who to do that in a way, which is most consistent with good patient, care and rigorous attention to the research activities. So, I think in general, I mean, compared to 20 years ago I think our relationship with the FDA is much stronger.

So, I think from a rational point of view you have a genetic disorder. There's a mutation that needs to be corrected. What you want to do is introduce a wild type gene into the patient and we had viral vectors to do that. It seemed like a very rational step to take. And French Anderson who was one of the pioneers in this at the NIH used to say, "His goal is to have a syringe injected into the patient one time and correct the defect and have the patient a few weeks later walk away with a lifetime ahead of no genetic disorder. It turned out to be much more complicated. I mean,

I remember being at a gene therapy meeting in the mid-90s and I was asked to make some introductory comments and I -- and I said, "You know, we are in the situation of having a baby that we love -- this idea of gene therapy -- and we've nurtured it, we fostered it, we've done everything we could to get it going. And it's now four or five years old and it's not walking and it's not talking and it's not producing any of the outcomes that you expect in a four or five year old and we're all starting to get really nervous." So I think your description of how disappointing it was that gene therapy didn't play out in a much more rapid and simple way was true. I mean, NIH was a leader in starting gene therapy and I think maybe NIH was the first to realize that this was going to be a tough, long road to hope. Now, things have -- more recently we've had some successes and I think cell based therapies are starting look attractive. I remember when Francis became director one of the things that he talked about was the need to think beyond gene therapy to small molecule therapies that could either stabilize proteins that might be unstable as a result of mutation or provide ways of bypassing mutational effects and so on. From a purely pharmacological point of view pharmaceutical therapies were going to be much more cost effective and probably would work well in a lot of genetic diseases. And we've kind of been -- because we were so taken with gene therapy I think we had been ignoring that likelihood for quite a while.

Well, I wouldn't blame the press. I think scientists were enthusiastic too. And not -- maybe they were deceiving themselves but I think their enthusiasm was based on the extreme rationality of the approach. It made sense. We just didn't have all the tools that we needed. And I would say in general that's true for biological sciences. They're -- it's not like we talk about moon shots. But when knew where the moon was and we knew celestial mechanics and we knew what was needed in terms of building rockets. We don't have those pieces for most important biological problems. So, gene therapy -- I think it just was -- it was -- it was premature. Now, I work in the field of cancer drug resistance and every time someone comes up with a new therapy for treating cancer there's enormous enthusiasm in small molecule therapy that's targeted to specific defects in cancers based on genetic analysis, immunotherapy. Huge excitement. It's in the press. It's touted by the scientists. And I have the slightly sadder but wiser view that drug resistance is going to be a problem no matter what you do. We have a, you know, very heterogeneous group of tumors and they're going to become resistant and we have to start thinking about that. We'll make incremental progress but the likelihood that they'll be a silver bullet is pretty low. And I think that's true for genetic diseases as well. We're not quite there yet. Now, CRISPR -- new excitement at CRISPR. I think, you know, when we start introducing it into patients to correct all their genes that we'll run into problems [laughs].

Right. So, I mean, you asked the question about the press touting a treatment which turned out not to be as satisfying as we hoped it would be. I think that the press of course is interested in selling, you know, their papers and their magazines. But also, in selling a sort of enthusiasm about science and I think it's not the end of the world that the public be self-educated enough to realize that everything they read is not necessarily likely to come to pass. At least not immediately. There is progress over time. I think that's the important lesson and we just have to be patient.

Male Speaker: So, when I had Maynard Olson in here a couple weeks ago.

Michael Gottesman: Ah, you got him in here.

Male Speaker: Oh yeah.

Michael Gottesman: That's great.

Male Speaker: Oh yeah. He answered -- I had a whole list of questions, you know, very detailed -- he answered four of them for about two and a half hours.

Michael Gottesman: [laughs] Is that right?

Male Speaker: He -- and he actually working on a history and philosophy of science. He's very engaged. He has a bunch of my books. He said that one of the things that -- when he was writing that Albert's report that he made sure to do -- particularly in regards to sequencing is he didn't overhype it.

Michael Gottesman: Right.

Male Speaker: And he thought that that was key to the success of the human genome project -- something like that. You don't over hype --

Michael Gottesman: Well, Maynard is both a very wise and a very -- and really an architect of a lot of the structure of the genome project in terms of how we go about doing business. So, yeah, I think probably you got a good two and a half hours of important information from him. That'd be my guess.

Male Speaker: The -- but his comment about hype is, I think all of a sudden [unintelligible] where he says that basically hype -- and I think he was thinking of some one person in particular where hype is sometimes damaging to --

Michael Gottesman: It can be. But hype is -- has a negative pejorative of, you know, kind of sense to it.

Male Speaker: That's how he framed it.

Michael Gottesman: Yeah. I think informing people about exciting new advances even though the outcome of those is yet to be determined is not necessarily a bad thing. I think that -- I remember just at the laboratory level when you're designing an experiment the excitement and enthusiasm that you have about each experiment is an important aspect of kind of sustaining interest in science. In the back of your mind you know you need to do the controls and they may turn out not as you expect. But it's fun to kind of hope for each experiment that there'll be something new that you learn [laughs]. I mean, a lot of science is just the excitement, the exuberance, the fun of doing the experiment and hoping to get a clear result.

So we had a war on cancer, right? And that also was a bad metaphor, because wars you win or lose. Although we've, the United States, we've discovered that there has -- is an intermediate stage when you get into ours. And I think the history of that and the fact that a huge -- that the money that was invested in the war on cancer had a huge payoff in terms of development of molecular biology. Most of neurobiology wouldn't have been possible without the war on cancer and so on. The more the public understands that investments in science have broadly important consequences. There's a discussion now about investments in HIV/AIDS research. And, you know, why is it ten percent of the budget and you know. But you can track a lot of very important discoveries that may not be -- may not have resulted in the cure of AIDS yet, but have implications for all kinds of science. So it's hard to convey that because we live in a very sort of product-oriented society where you invest a million dollars, you expect to get a million dollars back on the investment you made. But in fact in science, money that's invested in good quality science always pays off, but may not be in the arena that you're investing in.

Well I think Francis made the point recently that CRISPR, which is a technology that came out of bacterial work, is in fact the most likely for example to lead to a cure for HIV/AIDS. If you want to clip out the virus, that's the way to do it. And not a single dollar of AIDS money was spent on that technology. So that's an example of where an unexpected technology in a different field is going to have implications.

Right. So remember the NIH is a very federated system. And funding goes to each of the institutes to support research. The institute director is determined to a great extent how they spend that money intramurally and extramurally. And when I say to a great extent they can't suddenly increase or decrease the size of their intramural program, because there's an overall target figure for the NIH at the size of the intramural program, which is now on the order of ten to eleven percent, in that range. So each institute determines how to spend the money, and the scientific director becomes the guardian of the funding for the intramural program. There's a close relationship between the scientific director and the institute director, and I meet twice a month with the scientific directors to discuss how we can create an environment at NIH that enables their work that they're doing. It's unheard of basically for me to tell a scientific director what science they should do. Except we oversee the quality through the outside review process. But the specific directions are determined by the scientific directors. Now we recently had an outside review, which under the province of the advisory committee to the director. And they made a series of suggestions, some of which were that we should try to focus on a few areas in which we had great strengths. And so we as a community have decided that we want to make more investments by recruiting people, by maybe providing core resources in certain specific areas. One of which is the intramural version of Precision Medicine, which is very differently conceived than the more global Precision Medicine project that Francis is overseeing in the extramural community.

Okay. So we've had a lot of discussions about what we can contribute, and one thing that's obvious is the strength of the NIH clinical center is -- or the genomics here obviously, but it's in the phenotyping of patients. And the genetic information only is interpretable in the light of the phenotype. So not every single mutation will have a one on one correlation with a phenotype. There are -- there's this issue of penetrance and mutations and other mutations and the genetic environment of the person that determines whether genes are expressed or not expressed, environmental influences and so on. And so to make Precision Medicine work, that is to be able to figure out whether this mutation leads to this phenotype. The phenotyping is at least as important as the genotype. So we have already existing, terrific databases and phenotyping. And we study about 1100 different human diseases that are genetically determined in the intramural program. So we have cohorts of patients and so on so forth. The investigators who study those diseases have little or no information about whether when they have a specific genetic disorder, what the general population looks like in terms of the existence of those mutant alleles, so those alleles that cause disease but are heterozygous in the normal population. So what is the effect of that on the phenotype of the patient? The heterozygotes are much more common than the homozygotes for recessive genetic disorders. And secondly, whether other alleles in those diseases, polymorphisms in the gene, have any effect at all. And there are enough isolated examples of people presenting with a minor kinds of disorders who have defects in -- minor defects in genes in which major defects cause real disease that -- we have reason to think that if we understood the range of phenotypes and alleles associated with specific genetic disorders, that would be useful. So the proposal, which came from Les Biesecker, who was a senior investigator, obviously, in Genome, and is interested in kind of collecting information.

You're smiling so I guess you know the rest pretty well. And Richard Siegel who's interested in inflammation, immunology, who was the clinical director in IMS. To for all the genes, or many of the genes that interest us, to have a standard population of apparently otherwise normal people to be able to ask for this specific genetic disorder, what are the -- what is the phenotype of alleles in this gene in a more general population? And the idea would be so if you're interested in a gene for chronic granulomatous disease, which John Gallin works on. It's an NADPH oxidase defect. There are a number of different disorders. What do the heterozygotes look like? I mean you know that in family trees because you generally have the parents, but in a general population, you have no idea. So what do the heterozygotes look like, and what do people with other alleles in that gene look like? So the idea would be to bring those people in, and their calculation is you need about 10 to 20,000 genotypes to be able to do this. So you bring those people in, you study in the clinical center, and suddenly you have a lot of detailed information for specific disease chains about what the range of phenotypes there are. And if there's something wrong, if someone comes in and has something wrong with one of those genes, what is the likelihood that they'll have a measurable phenotype? Now to some extent you're taking people who think they're normal and defining for them perhaps a phenotype that they didn't know that they had. And it always creates some anxiety, and I think when we do informed consent, we're going to have to tell people that they may learn things about themselves that they'd rather not know. But on the other hand it will give us much firmer data on which to do Precision Medicine. That is to say this phenotype, this genotype corresponds to this phenotype. So it -- we're going to start on a relatively small scale. I think one of the things we need to do is we need to start to genotype at least do exomic sequences on all of the patients who come into the clinical center so we have that based off information. And we're starting to collaborate with some other groups that may have more genotypes that we can -- that -- where there's an interest in getting phenotypic information. The other thing that we can do at the NIH is during the million genotypes that are being conducted, we will come up with some genotypes that are mind boggling in one way or the other, where we say wow, how could this be. And we will hopefully be able to bring those patients in and do really detailed phenotyping in the clinical center to find out whether those phenotypes have effects and whether the predicted effects occur, whether other effects occur.

So, Richard is, officially, the deputy to the Deputy Director for Intramural Research, and the Deputy Director of the Office of Intramural Research. And he really is my alter ego. So there's hardly any issues that he doesn't participate in. We have meetings, I would say, several times a day. We have office meetings with the senior people in the office three times a week, and we set an agenda which covers all the major issues that are coming up. And those tend to be both reactive, because it's a big enough organization, we're talking about 15,000 people, so there's always something happening in one or the other domains of the NIH that we need to deal with. But also we hope to be proactive, and, you know, one of the issues of course is always spending all your time responding to emergencies, and not having time to think kind of long-term. This past couple of years we've been working on some long-term planning, which is partly in response to what I would call the flattening of the NIH budget over the last ten years, which has affected the Intramural program. You start to understand what inflation means when you're losing 4 percent or 3 percent of buying power every year for ten years. So we're about 30 percent smaller in terms of what we can accomplish than we were ten years ago. So we have to I think, reconfigure how we think about what we can do in the Intramural program. We always say we can do anything here, but we can't do everything here. So we have to decide what emphases we want. In the context of this federated structure, in which each institute has pretty much control over resources and so, providing a leadership role in that situation is difficult. And Richard and I basically work together on these things. We have a very frank and open relationship. If he's unhappy with some direction that I'm going, he'll tell me, and if I need help in some area, I certainly engage him all the time. So we have a very close relationship, and it's been wonderful working with him. He's just -- he has an enormous, you know, you're a historian, he has this enormous sense of the history, of what has gone on in Building One. At the moment, he's the person who's had the longest tenure in Building One.

And he goes back, you know, to Jim Wyngaarden, and Frederickson, and all the people who've been there since I've been Director as well. So it's -- he's both a resource and also an asset to the program, because of the way that he's able to get things done. It's quite amazing.

Sure, sure. So, actually this began as a discussion that Francis had with his senior leadership about ways in which we could improve the science going on across the NIH, not just intramurally but extramurally as well. And I thought that, because of the reason I gave, which is the flat budgets and what has been a revolution in the way we do science, both technically and conceptually, that it was time to really rethink what we could do in the Intramural program. And with back-and-forth involving me, and Francis, and involving Larry Tabak as the principal Deputy, we worked out a process which began by asking each institute to come up with their long-term plans. Now, the context of this is that there are supposed be, every five to seven years or so, or in many cases up to ten years, a review at the institute level of where their Intramural program is going. They bring in outside committees, and they go ahead -- people have been doing that for the 23 years that I've been Deputy for Intramural Research. We'd gone through more than one full cycle of each institute, kind of thinking ahead. This is what we call blue ribbon panel reports. But this was an opportunity for us all to do this simultaneously. And so each of the institutes set up an outside committee, consisting of people from their Boards of Scientific Counselors, their External Advisory Council, and outside experts who they brought in. And they said, you know, "What should we be doing that we're not doing? What should we stop doing that we're doing? How can we have much more impact than we currently do?" And each institute wrote a report. Some of them were relatively short and concise, and some of them were lengthier. The NCI report was the longest, but had the most to say, the most resources to deal with. And we collected all those reports, we had what I think was a historical meeting, which included the clinical directors, the scientific directors, the institute directors, and the executive officers. We all got together in this building, 31, and we tried to pull out the threads of what the common features were of those reports. We had a day-long discussion, it was, I think, quite valuable. And that information went to the Scientific Director as a kind of working group to figure out what -- how we wanted to move forward. My office assembled a report based on the reports of the individual institutes, and what we thought were the priorities for the NIH. And that report became a document that went to an external advisory committee, which was a subcommittee of the Director's Advisory Committee, to the Director. And that was last summer, they got our report. They themselves did due diligence, came to the NIH several times, talked to a lot of people, and made a series of recommendations which were, I would say, parallel to the ones that we had come up in our report, but had some different emphases and different elements. And we got that report, and were able to pull together what we had been thinking, and what the outside group had been thinking, to what I would call a long-term vision for the Intramural program. It involved emphases on certain aspects of our strengths, emphasis on certain kinds of science. As I said, we can do anything, but we can't do everything. Focusing on those areas in which we already were poised to make advances, but by bringing people together across the institutes we could do more. One example is in the area of chronic inflammation, where -- NIH has probably around 400 people who do various aspects of immunology, but we didn't have an organized way of getting people together. There were obviously collaborations, but thinking about specific kinds of problems. And we're still in the process of figuring out how best to do that. But we identified that area as cross-cutting, affecting all the institutes. We'd already established a Center for Human Immunology, which was located in the Heart Institute. And they were capable of analyzing different aspects of the human immune system, but not focused on specific medical issues, disease problems and so on. So that's just an example. We had human microbiome, drug-resistant microorganisms, RNA biology, and RNA as both therapeutics and targets for therapeutics, it's an exciting area. And what we imagined is that with this sort of shortlist of things that we wanted to do, would help drive our recruitments, would help us create teams, would help us determine what kind of instruments and resources we needed to get things to work. And so I think it was a very useful process, and kind of is a way of helping me set priorities for what lies ahead. The Advisory Committee to the Director heard our response to the report, and was very enthusiastic, endorsed it I would say wholeheartedly. And I'm in the process now of trying to put together more detailed implementation plans, so that when I talk to them again, I can say, "Here, so here's what we wanted to do, and here's what we've accomplished so far." One, I would say, one current barrier is, one of the strong recommendations, and our good friend Eric Green spearheaded this, was that there'd be a fund available to the Deputy Director for Intramural Research that could be used to stimulate whatever it is that that Director thought would be an important way forward for the program as a whole. Creating that fund is not trivial. The institute Directors decided the best way to do it was if and when the NIH budget increased, that a small percentage of that increase would be taken as a tithe to be used for that purpose. And we're in the process of discussing that now, because this year the NIH budget did increase, and the question is how much, and when, and so on and so forth. So I'm working on that with my colleagues and the scientific Directors.

The increase for the Intramural Program is pretty small. A fair amount of it is for the mandatory salary increases, which we have not had for, as you know, many years, with three or four years of basically frozen salaries. And some of it is catch-up. So if you look at what's happened over the years, equipment purchases, for example, have fallen pretty dramatically. So as always happens when budgets are tight, capital equipment goes down. It's always been an important element to the Intramural Program, to have state-of-the-art equipment. So I think there's a catch- up period in which people are trying to use whatever additional funds they have, at least in the one year, to make up for those years pretty much of starvation. So there's not a lot. The increase is not really even inflationary. It's close to inflation for just this year, and that doesn't cover the ten lost years. So it's not really a huge amount of money, and I think we're trying to figure out how best to use what's available to the Intramural Program. And of course, each institute determines how much money their Intramural Program will get, with the overall increase being, you know, relatively modest.

So as I said, we had flat budgets for many, actually more than five years in the Intramural Program. And then a few years ago, there was a sequestration of around 5 percent, a little more, of the Intramural budget. And that happened in the middle of the fiscal year, so that if people had been spending at the previous year's rate, it actually doubled the effect of the sequestration. So it was like a 10 percent decrease over a six-month period, basically. And it totally stopped new recruitments, for a while, slowed them down. And, remember this is an era in which we're desperately trying to increase the diversity of the workforce. And that requires new hires, that requires new efforts to keep people who are already here. And all of that was sort of a brought to a standstill by the sequestration. It's had profound effects on the Clinical Center. That budget, you know, even to increase it by inflation for cost of drugs, and manpower to run the hospital, and so on, the way other hospitals do, has been very, very difficult. And I think John Gallin, who manages the Clinical Center, has had a really difficult time getting the resources he needs just to have a state-of-the-art, cutting edge hospital. So there are lots of negative things. You may remember at the time of the sequestration, a lot of the press was focused on the Clinical Center, on the impact on the Clinical Center. Hiring the very best possible physicians, making sure that the pharmaceuticals were state-of-the-art, assuring that the capital equipment budget was up to date, and equipment wasn't out of date. All of that very difficult, when you're actually having your budget cut.

If you interview intramural scientists, they to a person will say the kind of science they're doing would be impossible to do elsewhere. Very long-term projects, the grant system is limited to four or five years, for a grant. And lack of productivity in that period makes it very hard to renew the grant. Whereas an intramural scientist can conceive a project that could last 20 years. Develop a vaccine, for example. Uncover the cause of a disease which previously had never been studied before. Develop an animal model in a totally new system that we've never had before. So those kinds of things can be done in the Intramural Program, because there's some guarantee that if the science is heading in the right direction, that support will continue. And just to remind you, we have a pretty rigorous review process, but it tends to be retroactive, rather than proactive. That is, people are judged on their progress over the last, in our case, four years.

And, although it's important to hear what they're going to be doing, particularly if they're early- career scientists, their track record and their ability to solve problems is considered more heavily than it might be in an extramural grant application. So that allows people who are doing well to continue to do well. Those who despite all the support they get are unable to produce anything of value, will find very quickly that their resources will dry up. But we tend to be a little more patient, particularly with people who are extremely talented, and giving them a chance to be successful. So the totally distinctive features -- and I won't say unique, because it's possible to recreate these with enough energy and money and so on in other organizations as well. I think the Clinical Center is a pretty distinctive feature of the Intramural Program, and it is centered in the middle of our campus. It's hard to miss it, when you come in every day, and I think many of the people who come to the NIH are thinking, "One day, what I'm doing in the laboratory will have relevance to what's going on the Clinical Center." And so we try to learn from the patients who come here, bring their problems back to the laboratory, and take the information from the lab and turn it into a new understanding of disease, and maybe new treatments of those diseases. And that's, I think, in everyone's mind, every day. I think -- that's an unusual circumstance in any academic organization. You asked how -- whether we would compete most with industry, or with academia, and I think there's no question we're part of the academic structure. People come here from academia, they go back mostly to academia. Occasionally, we'll have people go off to industry, but I don't think at any higher rate than academics go into industry. And it's usually people who have been reasonably successful, and are starting to think, "With the resources that industry have, and the targeted approach to therapeutics, I'm much more likely to get from where I am now to a drug that patients will be able to take in a limited period of time than if I go to academia or stay at the NIH." We are pretty effective in tech transfer. I mean, we have a lot of effective products that are out there. And I think it's partly because virtually everyone who's here is always thinking, in the back of their mind if not in their actual laboratory work, you know, how will this lead to some new understanding of human disease?

And I think if you expanded that to the top 200 scientists at the NIH, you'd find that the history of their science also would have been difficult to support on the outside. Now there are lots of well-established extramural scientists who have had continual support from the NIH for 20, 30, or 40 years. And many of them are truly outstanding scientists. So it's not unique at the NIH that we have long-term support, but it is the rule rather than the exception. And I think that creates an environment -- Well, one thing, it creates an environment in which people are not competing with each other for resources, and so it is totally comfortable to go down the hall or go into another building, and get help from somebody which is quite substantial, and doesn't have a lot of strings attached. It's really easy to go from an idea to an experiment within a matter of hours or days at the NIH, because there's always an expert someplace who has either the piece of equipment, or can point out the controls that you need in your experiment, can give you advice which is really valuable in moving science forward quickly.

Well, so she was a mentor, an advisor, a role model. And I remember, there was a transition as you may recall in my life, when I went from being a laboratory rat to having more and more administrative responsibility. Some of that transition was a period when Harold Varmus had already been named, but Ruth Kirschstein was the Acting Director of the NIH. And she called me in to help serve as a liaison between the Marks Castle Committee that was reviewing the Intramural Program, and the Intramural Program. And then when Harold became Director, he asked me to stay on as Deputy Director for Intramural Research. So Ruth was quite an extraordinary woman in many ways. As you may know, we -- I was partly responsible for this, we put together a biography of her, which is available free online, Amazon [inaudible], I think, that anyone can read, and there's a few hard copy versions which are real collector's items, that talk a little bit about the forces that shaped her. She was early on one of the first women medical graduates of Tulane College of Medicine. And she was interested very early on, I think, in public health issues. So she had this kind of basic inclination to want to do something which would be seen, and would be effective in improving the public health. And she got involved when she was at the FDA, Bureau of Biologics, in the Cutter Incident, which was related to contaminated -- there were polio vaccines contaminated with, in this day, in the era of the Salk vaccine, with live virus, and there was real danger that there would be a mini epidemic owing to the contaminated vaccine. And that -- she played an enormous role in kind of uncovering and dealing with that incident at the FDA. And I think it's one of her proudest moments, she talked about it quite a lot in later years, as an example of how important it is that the government oversee the conduct of, not only of medical research, but of medical practice. So Ruth moved, as you know, to the NIH, and was the first woman director of any institute. Directed a really important institute, the National Institute of General Medical Science, which to some extent was the predecessor to the Genome Institute, [inaudible]. So a lot of ideas about the human genome, and about collecting data sets and so on, came out of those early years with Ruth. She was by nature a kind of cautious person. And the field, which was exploding with revolutionary ideas, I think needed leadership that was bolder. And I think she didn't put up much of a fuss and realized, when the Genome Institute was being created, that this was a reasonable direction to go. I think she harbored until her death, probably, a little bit of feeling that it would have been fun to be in charge herself, but she wasn't at that point, and I think that was appropriate. She was enormously devoted to the NIH. This is an anecdote which I don't know that anyone else has ever reported before, but she and her husband Al Rabson, who were called in some science article "the power couple at NIH." If it was power, it was soft power. It was power exercised through argument, persuasion and not in a heavy-handed way. But at some point somebody noticed that for many years, she hadn't taken any annual leave. And there was a little bit of a mini-investigation as to what was going on, and it was quickly determined that she hadn't taken any leave because she hadn't taken any leave. She had been working, she worked probably 18 hours a day, and she had been doing that every day for her entire career, really, at NIH. She was so incredibly devoted. She and Al used to go to concerts, at Kennedy Center, and she would bring, you know, two or three bags full of grants because she read every NIGMS grant, before she signed off on them. And she would bring them to the concerts at night, and look at them while she was listening to the music. She was an extraordinary person. And her sense of integrity, and particularly the importance of stewardship of federal funds, was bar none the highest that I've ever encountered in the federal government. Many people at NIH are quite, I think, concerned and devoted to making sure that the moneys that we get from the public are used most efficiently. But for her it was a religion. There was no waste, there was no abuse. Everything that she did was done modestly to make sure that nobody under her purview was ever accused of inappropriately using government funds. And I think that sort of stayed with me. I tend to be a little bit on the [laughs]. I try to be efficient in the use of government moneys. And part of that comes from Ruth. So when she invited me into Building One, we had this discussion about why I should want to do this job, as opposed to staying in the laboratory. And she said, "You know, problems that you solve in administering science are in some ways more complex and more interesting than problems in the laboratory." And I have to say, after doing this for 23 years, she's right, you know. They involve multiple variables, there are no controls. [laughs]. They're all intrinsically big data problems with small data points, and they have proved to be very challenging over the years. But not insoluble.

I would also say she had a special relationship with a lot of people in Congress, partly because of her longevity, because in the old days all the institute Directors used to testify before the Appropriations Committee. And she had a -- they really trusted her. I mean, talk about trust in public officials. When she said something, they knew it was precisely true. And that's, you know, incredibly valuable for an institution like the NIH, to have a reputation of that sort. And I think she kind of set a very high standard.

Right, so you can imagine that the change from how Varmus, who was a Nobel Prize-winning laboratory-based scientist, to Elias Zerhouni, who was a radiologist, in a different administration, Republican, not a Democratic administration. But who had a track record of -- you know, he was Vice President for Research at Hopkins, and he had a track of being able to marshal resources to effect change. And we had actually a very positive relationship from the beginning. One of the things I've done for every director that's come in is, in my initial meetings with them, I provide information about the Intramural Program, and I've said, "You know, I serve basically at your pleasure. And if you would like to have your own Deputy Director for Intramural Research, I'd be willing to step back, go back to laboratory. I keep hoping that will happen." And he laughed, and he said, "No, no, no, I've heard about you, I definitely want you to stay, I want to work with you." And then he started to talk about his profound respect for the Intramural Program, and certainly that won me over pretty quickly. One of the things that he used to say, and this may be an exaggeration, but I kind of like the analogy, is that doing science is like a voyage of discovery. Sometimes you set out in a ship, not knowing what islands or continents you're going to discover. And he saw the Intramural Program as sending out those ships into the great unknown, and needing maybe years of support in order to accomplish something. You find a new colony, you discover some new field of science. And the colonization of that particular field might be a combination of people who are already at the NIH. But extramural scientists who can apply their -- because of the way the grant system works, they have to know what they're doing. So they have to be on the island before they can actually accomplish it. In fact, in many cases they have to have already done what they're saying they're going to do, in order to get grant support. Yeah. Now reality, of course, lies between. I think it is easier for intramural scientists to set out on these unknown voyages. But extramural scientists, who by nature are as, I think, as creative and innovative as intramural scientists, use every means at their disposal to do the same kind of thing. So there's not a real distinction between the two, there's overlap. But the Intramural Program is set up to encourage people to set out on those voyages. But for me that analogy told me that he got it. [laughs].

And after that, we had a wonderful relationship. And he was very involved in the Intramural Program. He would come frequently to talk to the Scientific Directors. He would come to retreats in which we talked about science. And he very quickly learned a lot of things. And towards the end, when he stepped down, he actually spent some time as a visiting scientist in my laboratory. For a very short period of time, he used to come to our lab meetings. And we worked up a project using what's now called theragnostics, where you use diagnostic features of radiology to also disease. And we had a little project which didn't actually go anyplace, but it was something we were interested in doing in both diagnosing and treating breast cancer using approaches that he and I had worked up together. So we had a good scientific relationship, we had a good personal relationship. And I think I turned out to be quite a visionary leader for the NIH. We were very fortunate to have him. He established the Common Fund, which I think has been a very useful way of, again, pooling federated resources to be able to allow the NIH Director to move ahead on some projects. And I think, also, kept us together during a politically difficult time. You may remember the period when people were worried about stem cells, and so on. And he got us through the conflict of interest situation pretty well. And the other thing -- so Elias was known for his aphorisms, you've probably heard many of them. But one of the things that really stuck with me is, he said, "It's never the wrong time to do the right thing." So, you know, even if you've been doing things that haven't been exactly right, if you can figure out how to improve that, you shouldn't say, "Well, I'd rather do it the old way," you should find new ways to do things that I think reassure the public about stewardship at the NIH. And so conflict of interest came to that. Under Dr. Varmus, we'd worked out arrangements in which people were allowed to interact with industry, to consult, to receive funds for that, so long as they were very careful in separating their official duties from their outside activities. And all of this was kind of monitored. What happened during Elias's period is that there was an incident involving one of our scientists, who was both providing materials, fairly unique biological materials, as part of his official duties, and at the same time serving on, for the company, on one of these speaking panels, and receiving hundreds of thousands of dollars in funds. So the appearance was that he was receiving the money in return for his willingness to provide these unique patient materials. I think the reality was these were sort of separate activities, but what had drove home was that what reality is, and what perception is, in terms of conflict of interest, are not distinguishable in the government. So even if the scientist argues, "Well, what I'm doing is not influencing in any way these other activities I have with the company," any reasonable person might perceive that there could be an influence. And so one of the jobs that I have is to convince scientists that it's both reality and perception. Perception becomes reality, for government ethics. And so we ended up setting up a very, I would say, rigorous system, in which people simply don't consult for money with companies. This is, I would say, probably that is a unique feature of the Intramural Program. And I think it's added to the public trust in what we produce in our scientific publications. Because there are no financial connections between any of our scientists, and the companies with which they're working.

Oh, I mean, just to clarify my role, I mean, my role is to be the extension of the Director, in the Intramural Program. So when the Director says, "We want to emphasize XYZ," my role is to figure out how to take this complicated organization, and move it in that direction. It's not going to jump, you know, on a dime to do what's expected, because it's a big battleship that has to be turned. But my role is to carry out the policies of the NIH Director. And the NIH Director's role is to support the mission of the NIH, which is still a wonderful mission. To do research, to improve the public health, and train the next generation of scientists. And I think each Director brings a certain, both a personality and an intellectual direction to that specific mission. As you mentioned, Francis thinks very broadly about the revolution in the way we do biology, about bringing to bear as quickly as we can the tools that we have to solve really important problems. He's always been, in my mind, as much a physician as a scientist, even though he's a wonderful scientist. And he thinks very broadly, and is enormously effective. I mean, the Genome Project being an example. Not anyone could have brought that to fruition. And, you know, when we were recruiting Francis -- I was on the search committee, it was clear that he knew exactly what needed to be done. Not precisely, in terms of, you know, day to day, but he knew the direction that we had to move, and he knew how to get the forces to work together on this, and that he was exactly the right person for that job. And when it came to be time for him to be NIH Director, I think he brought the same really laser-like focus on being able to have products that would demonstrate that the money that the public was investing really was being well-invested. Not the kind of criticism that that approach gets is that, you know, science is open-ended, you have to give people the freedom to do whatever they want to do, you can't be so product-oriented. On the other hand, that doesn't go over so well with the Congress and with the public. So finding that balance between allowing people to do the creative, innovative science that eventually, like Chris Burr will clearly have application, and applying the science we have to really important problems is the trick of being a great leader. And I think Francis has balanced them quite well. And I'm pleased that I've been able to help do that, within the Intramural Program.

Right. So it's hard to talk about Eric without talking about his energy. So his energy level is enormously high. And just by force of personality, he brings a lot of people along with him. So he really leads by example. Eric, I think, from the very beginning, in his own career, has been really been a force for understanding that having large data sets in themselves were enormously valuable. Large, high-quality data sets, obviously. NISC is a great example of his saying, "Okay, we can do this for the Genome Project, so let's do it for the entire Intramural Program." So one of the things we haven't actually discussed is the role that Genome has played in the Intramural Program as a whole. And sequencing -- providing mega-based sequencing facilities is an obvious example. But the whole aspect of what we used to call reverse genetics, which I always thought of as genetics, which is the ability to position the cloned genes that are associated with disease, was really started within the Intramural -- the concept preexisted. But the success, the first eight or nine or 10 genes that were cloned, were cloned within the Intramural Program. And the technology to do that very quickly spread to the other institutes. Some of the core facilities that were set up within Genome were way ahead of what would have eventually happened, but much more slowly in the Intramural Program. So it really was a catalyst to stimulate a revolution in science that might have taken a lot longer. And I think in a way, we would have been in serious trouble intramurally, had we not had the Genome Project projection as an intramural program here. It really made a huge difference at a time when we were at risk of becoming a backwater in human genetics, and put us at the forefront rather than the back. And all the other institutes quickly adapted the technology that was needed. I mean, there are probably 1,200 diseases that are studied in the Clinical Center. They approaches that were being used were relatively primitive, and suddenly we had new tools, and they were available to everybody.

Right, right. So, maybe I'll differ with you a little bit. I think one of the strengths, always, of the Intramural Program, had been our desire to quantitate a lot of the great -- so it started with instrumentation, some of the things that we take for granted. The [unintelligible], for example, used to able to look at a culture of cells and say, "Oh, there are a lot of cells there." But being able to count them, and distinguish them, counting, counting, quantitation, is an intramural contribution. People here appreciated that this technology needed to be advanced. The first fluorimeter and spectrophotometer, for measuring things, intramural. So I think there's been a history, intramurally, of quantitating things. Another example, which I think is little appreciated, is the work that Jennifer Lippencot-Schwartz did. So cell biology was a fun observational field in which people did electron micrographs, and optical images, and they said, "Oh, look, isn't that interesting?" Jennifer was one of the first cell biologists to start to measure, you know, the flux of molecules from one sub-cellular compartment to another, and get real numbers, and start to see which pathways were more efficient, and which were less efficient, and so on and so forth. So I think we have a long history of quantitation. Now, the kind of quantitation you're talking about is population kinds of quantitation. And I think one of the interesting challenges now, and I haven't thought through this entirely, but I think it will be an issue for all of human genetics, particularly because I'm a cancer researcher, is the heterogeneity that we're beginning to see in cancer, in tumors. So if you sequence a thousand cells in a tumor, each one of them actually has a different genomic sequence. Their RNA expression differs from tumor to tumor. So you mentioned Maynard Olson, you know, being a stickler for accurate data. So depth of sequencing begins to tell you, for example, if you're interested in acute myelogenous leukemia, and you get a bunch of cells from a patient, and you actually, you know, get a hundredfold, or a thousand- fold coverage of the genome, you start to see these minor features, which of course are the basis of drug resistance, and so on and so forth. So I think we're -- quantitation, always important. But I think population-based studies are being replaced by cell-based studies. And I know Francis is particularly in his own laboratory across the NIH, is interested in single-cell kinds of analyses. So we've sort of come full cycle, taking large data sets and averaging them, and understanding them, to looking at unique individuals and unique cells within those individuals. And I think we'll learn a lot of biology by doing that.

Well, one of the things that Elias used to say is, "Longevity doesn't make a thoroughbred." [laughs]. So I would hope it wouldn't be my longevity. [laughs]. I think probably the ability to get a diverse set of really talented people to work together. And I'm hoping, because my legacy's not quite finished yet, that the diversity aspect of the workforce, of bringing talent in. So one of the questions you had kind of asked me, which we didn't discuss, was about physician-scientists. And I think I'd like to make the point that I think that the Yellow Berets, at the time when people were either going to the Korean War or the Vietnam War, but came here instead, unearthed this huge talent pool that otherwise would have been practicing medicine, I might have been practicing medicine, someplace else, and gave them an opportunity to apply their brains to really interesting problems in biology. I think there are other huge talent pools out there that we're not tapping. Huge populations. I'm really worried about women in science, because I think even though we train women up to a certain point, postdoctoral point, 50 percent women, they start to drop off pretty dramatically after that. And I think all of that is creative talent that isn't really working on independent scientific projects. And for sure underrepresented minorities. So Hispanic and black and Native American populations, of whom only a very small percentage are ever going to end up having the opportunity to do science. Those are people we need to tap, because they're this enormous talent. I mean the Yellow Berets have an extraordinary track record of success, by any standard, you know. Nobel Prizes, and truly seminal discoveries in science. Because they brought a perspective which was different to a field which was, you know, already established. So I think if I had a legacy, I'm still working on it, it would be, you know, "He brought new talent into the pool of people who are working on difficult scientific problems."